

# Five-Year Safety Evaluation of Maraviroc in HIV-1–Infected Treatment-Experienced Patients

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**Background:** Maraviroc is unique among approved antiretroviral drugs in targeting the host-cell chemokine coreceptor type-5 receptor. With its novel mechanism of action, we sought to describe the 5-year safety profile of maraviroc.

**Methods:** Two large phase 3 studies of maraviroc enrolled HIV-infected treatment-experienced patients and followed them up for 5 or more years. Survival and selected clinical end points were identified and assessed.

**Results:** A total of 938 enrolled patients received maraviroc-containing regimens. Rates of death and selected clinical events (eg, hepatic failure, malignancy, and myocardial infarction) were low during follow-up.

**Conclusions:** Maraviroc was generally safe in treatment-experienced participants for >5 years.

**Key Words:** maraviroc, CCR5 antagonist, HIV, antiretroviral therapy, safety, treatment-experienced patients

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## INTRODUCTION

Maraviroc is a first-in-class selective chemokine coreceptor type-5 (CCR5) antagonist that demonstrated antiretroviral activity in early phase 2a studies of HIV-infected patients with CCR5-tropic (R5) virus.<sup>1</sup> Maraviroc has a unique mechanism of action among approved antiretrovirals in binding to a host protein, the CCR5 receptor, rather than a viral target. Maraviroc binds to the CCR5 receptor and prevents the interaction of the external membrane glycoprotein of R5 HIV-1, gp120, with the host cell receptor. Given the unique mode of action and use of a host-cell target, initial concerns existed about the potential safety of CCR5 antagonists, including maraviroc.<sup>2</sup> Also, early development of other investigational CCR5 antagonists demonstrated potential class-specific effects: aplaviroc was associated with severe hepatotoxicity,<sup>3</sup> and further clinical development was stopped; vicriviroc was initially associated with malignancies in a phase 2 study,<sup>4</sup> although this was not confirmed in larger phase 3 studies.<sup>5</sup>

In HIV-1–infected treatment-experienced patients with R5 virus in the MOTIVATE 1 and MOTIVATE 2 phase 3 trials, maraviroc together with an optimized background antiretroviral regimen demonstrated superior 48-week virological efficacy compared with placebo with no significant safety concerns<sup>6</sup>; these findings led to US Food and Drug Administration approval of the drug. Follow-up results at 2 years demonstrated sustained antiretroviral activity and no new safety concerns.<sup>7</sup> Given the unique mechanism of action of CCR5 antagonists, and the potential for longer-term safety issues, the US Food and Drug Administration requested extended 5-year follow-up for all study subjects receiving these compounds. In this study, we report the pooled safety findings from the MOTIVATE 1 and MOTIVATE 2 phase 3 studies for >5 years, the longest-term safety data available with a CCR5 antagonist.

## METHODS

MOTIVATE 1 (NCT00098306) and MOTIVATE 2 (NCT00098722) were identically designed, parallel, randomized, double-blind, placebo-controlled, multicenter phase 3

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studies. MOTIVATE 1 was conducted in Canada and the United States and MOTIVATE 2 was conducted in Australia, Europe, and the United States. Eligible participants were treatment-experienced patients, aged at least 17 years, who were infected with R5 HIV-1 (as documented by the original Trofile phenotypic coreceptor tropism assay), with screening plasma HIV-1 RNA levels >5000 copies per milliliter. Patients were randomized to receive the equivalent of 300 mg of maraviroc once daily, 300 mg of maraviroc twice daily, or placebo, depending on the planned use of concomitant antiretroviral drugs and other concomitant CYP3A4-active agents, together with an OBT regimen. On the basis of previous drug–drug interaction data, patients who used a ritonavir (a CYP3A4 inhibitor)-boosted protease inhibitor (other than tipranavir) as part of their background regimen received a reduced dose of 150 mg of maraviroc once or twice daily. OBT was selected individually by the site investigators on the basis of the antiretroviral history of each study subject together with the results of genotypic and phenotypic drug-resistance testing.

The studies were designed with the primary end point of mean change of HIV-1 RNA ( $\log_{10}$ -transformed levels from baseline to 48 weeks), and study subjects were unblinded to treatment assignment after all subjects completed the week 48 visit (or discontinued the study early). Study subjects were then offered to change to 300 mg of open-label maraviroc twice daily (or, as above, equivalent appropriate dose depending on concomitant medications) in an open-label phase of the study through 96 weeks, and then offered participation in a subsequent observational phase extending through 5 years after each subject's first dose of blinded study drug. Study subjects who previously discontinued the double-blind phase of the study early were offered participation in the open-label and observational phases. The study was approved by institutional review boards at each of the study sites, and all study subjects provided written informed consent.

Adverse events were identified and assessed real-time by the site investigators. Protocol-specified clinical events included AIDS-defining events, deaths, hepatic failure, infections reported as serious adverse events, malignancies, myocardial infarctions and cardiac ischemia events, and rhabdomyolysis. Protocol-specified survival and clinical events were retrospectively identified from the double-blind and open-label active phases of the study by mapping the investigator-identified adverse events to the clinical events of interest. Protocol-specified survival and clinical events were prospectively identified by the site investigators during the observational phase of the study. The incidence and both the raw event rate (based on total number of events and total exposure) and the incidence rate (using a conventional time-to-first event approach) were calculated for each event. Study subjects who terminated the study drug early and entered the observational phase “on study, off study drug” were not included in the analyses.

## RESULTS

Of a total of 3244 patients screened for the study, 1075 study subjects were randomized originally to the 2 phase 3

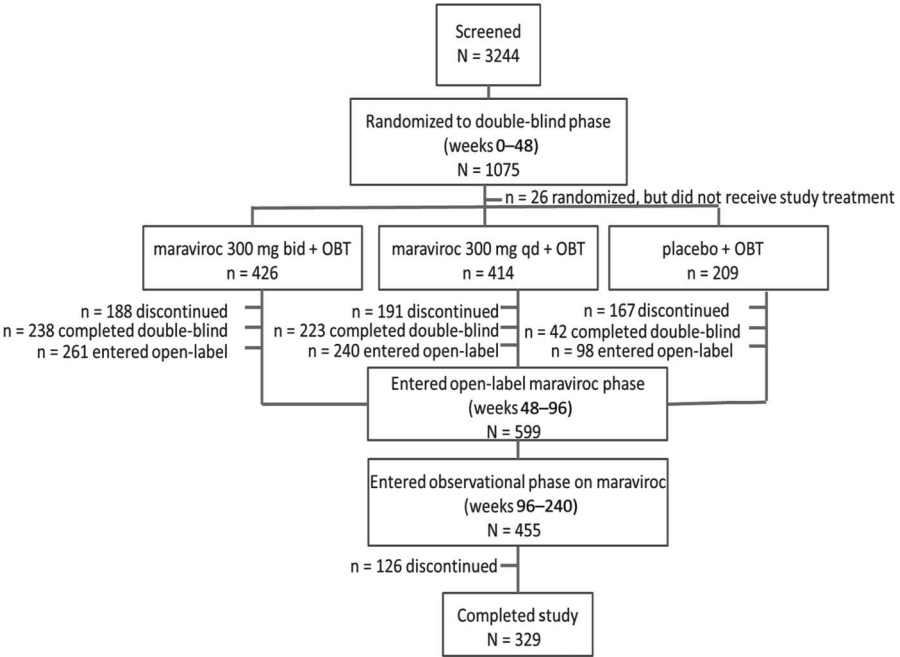
MOTIVATE studies, although 26 of them never received study treatment. Of the 1049 patients who received double-blinded study treatment, 426 patients received 300 mg of maraviroc (or equivalent) twice daily, 414 patients received 300 mg of maraviroc (or equivalent) once daily, and 209 patients received a matching placebo. Patient disposition is shown in Figure 1. Ultimately, a total of 938 study subjects (including 98 study subjects originally randomized to placebo) received maraviroc and contributed to a total maraviroc exposure of 2639 patient-years with a median exposure of 908 days (range, 1–2220 days). Demographic and baseline characteristics for the 938 maraviroc-exposed study subjects were balanced among the 3 study treatment groups, with the study population comprising >85% men, with >80% white, a mean age of 46 years, a mean prestudy baseline HIV RNA level of 4.8  $\log_{10}$  (geometric mean, 63,100) copies per milliliter and a prestudy median CD4 count of 169 cells per microliter.

Incidences and rates of survival and selected clinical events occurring during 5 years of the study are reported in Table 1. In total, 46 deaths were reported in the study, 8 occurring >28 days after discontinuation of maraviroc and 1 occurring at an indeterminate time. The causes of death were varied, with malignancies (28% of deaths;  $n = 13$  study subjects, including 4 with lymphoma, 2 with lung cancer, 1 with leukemia, 1 with anal cancer, and 5 with various other cancers), infectious diseases (17%;  $n = 8$  study subjects, including 5 with pneumonia of diverse etiologies), and cardiac/respiratory arrest (11%;  $n = 5$  study subjects) being the most common causes. Of the observed selected clinical end points, the most common were infections judged by the investigators to be a serious adverse event (12%;  $n = 114$  study subjects; incidence rate 4.7/100 patient-years), followed by AIDS events (8%;  $n = 78$  study subjects; 3.1/100 patient-years), malignancies (6%;  $n = 61$  study subjects; 2.4/100 patient-years), and cardiac events (3%;  $n = 26$  study subjects; 1.0/100 patient-years). Hepatic failure and rhabdomyolysis were uncommon (0.5%;  $n = 5$  study subjects each; 0.2/100 patient-years).

## DISCUSSION

Maraviroc was approved by the US Food and Drug Administration in 2007 as part of combination antiretroviral therapy for adults infected with CCR-tropic (R5) HIV-1 on the basis of 48-week results from the 2 phase 3 MOTIVATE studies.<sup>6</sup> Two-year follow-up, including a year of open-label maraviroc, revealed durable virological suppression and no new safety issues.<sup>7</sup> With extended follow-up for >5 years, we found the incidence of death and selected clinical end points was low in this HIV-infected treatment-experienced patient population exposed to maraviroc. Because HIV-infected patients take antiretroviral drugs for prolonged periods and are living longer, it is critical to continue to assess the long-term safety and tolerability of antiretroviral regimens. Few phase 3 antiretroviral clinical trials have formally assessed longer-term safety in study participants, with a few exceptions such as the STARTMRK studies of raltegravir with 5 years of reported data.<sup>8</sup>

**FIGURE 1.** Disposition of the study objects. Forty-five study subjects completed the double-blind phase but did not enter the open-label phase. One hundred forty study subjects did not complete the double-blind phase, but entered the open-label phase, including 29 from the maraviroc bid group, 29 from the maraviroc qd group, and 82 from the placebo group. One hundred forty-six study subjects who terminated study treatment prematurely and entered the observational phase as “in study, off study drug” are not included above. bid, twice daily; qd, once daily.



Although the labeling information for maraviroc contains a boxed warning for hepatotoxicity, a previous analysis of the maraviroc clinical development program revealed no increased hepatotoxicity compared with comparator regimens with follow-up of up to 96 weeks.<sup>9</sup> Our extended analysis of the phase 3 maraviroc studies found hepatic failure events were uncommon (n = 5, 0.5%).

Consistent with a previous report of pooled maraviroc phase 2b/3 studies with a median of 82 weeks of follow-up,<sup>10</sup> we found no excess occurrence of malignancies in maraviroc-treated patients after >5 years. The malignancy rate of 2.4 events per 100 patient-years in the present 2 treatment-experienced studies of maraviroc was comparable to the malignancy rate reported in a pooled analysis of the BENCHMRK 1 and 2 studies of raltegravir that enrolled a similar study population of treatment-experienced patients with advanced HIV disease failing their antiretroviral regimen who randomized to raltegravir (3.0 events per 100 patient-years) or matching placebo (2.6 events per 100 patient-years), in addition to optimized background antiretroviral therapy (OBT).<sup>11</sup> Although in a previous phase 2 study of another investigational CCR5 antagonist, vicriviroc, 12 (11%) of 113 of subjects who received vicriviroc developed malignancies,<sup>4</sup> ultimately 2 larger phase 3 studies of vicriviroc reported malignancies occurred rarely and without differences between the vicriviroc and placebo arms,<sup>5</sup> and therefore did not confirm an association.

In the current studies of treatment-experienced patients with virological failure on their prestudy antiretroviral regimen, the myocardial infarction/cardiac ischemia rate was 1.1 events per 100 patient-years. This was consistent with a previous analysis of ischemic cardiovascular events from this study with shorter follow-up.<sup>12</sup> Other cohorts have reported lower rates of cardiac events, for example, in the Data Collection on Adverse Events of Anti-HIV Drugs

(D:A:D) study, the rate of myocardial infarctions was 0.32 events per 100 patient-years,<sup>13</sup> and in a Kaiser Permanente cohort, the rate of coronary heart disease events (including myocardial infarction) was 0.35 events per 100 patient-years.<sup>14</sup> Two important differences between our study and these cohort studies are important to recognize: (1) our study used a broader definition of cardiac events that included cardiac ischemia and (2) our study population was treatment-experienced and had advanced HIV disease (median prestudy CD4 count <200 cells/ $\mu$ L) in contrast to the patient populations in

**TABLE 1.** Incidence of 5-Year Death and Selected Clinical Events in 938 Subjects Receiving Maraviroc (Total Exposure 2639 Patient-Years)

End Point	No. (%) Study Subjects	No. Events	Raw Event Rate (Events Per 100 Patient- Years)*	Incidence Rate (Events Per 100 Patient- Years)†
Death	46 (5%)	46	1.7	1.7
AIDS event	78 (8%)	98	3.7	3.1
Hepatic failure	5 (0.5%)	5	0.2	0.2
Infection judged to be a serious adverse event	114 (12%)	163	6.2	4.7
Malignancy	61 (6%)	79	3.0	2.4
Myocardial infarction or cardiac ischemia	26 (3%)	30	1.1	1.0
Rhabdomyolysis	5 (0.5%)	5	0.2	0.2

\* (Total number of events per total patient-years of exposure)  $\times 100$ .  
† Based on time-to-first event.

the D:A:D and Kaiser cohorts who were treatment-naïve patients throughout all stages of HIV infection.

The expanded access program for maraviroc enrolled and assessed 1032 participating patients who had a median maraviroc exposure of 174 days and found the safety and occurrence of adverse events were generally similar to the current MOTIVATE studies.<sup>15</sup> An additional study, the Prospective Observational Epidemiologic Study of Maraviroc's Safety (POEM; Study A4001067), currently is in progress and will continue to compare safety data for 5 years in 1500 patients on maraviroc with 1500 patients not taking a CCR5 antagonist.

In summary, in a population of HIV-infected treatment-experienced patients with >5 years of exposure to maraviroc, the incidence of death and other selected clinical events, including hepatic failure, malignancies, and myocardial infarctions, was low, and no new safety signals were reported. Maraviroc appears generally safe and well tolerated for at least 5 years in treatment-experienced patients.

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